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From Acenaphthenes to (+)-Delavatine A: Visible-Light-Induced Ring Closure of Methyl (α-Naphthyl) Acrylates

Theodor Peez, Jan-Niclas Luy, Klaus Harms, Ralf Tonner and Ulrich Koert*

Abstract: Disclosed herein is a visible light mediated cyclization of methyl (α-naphthyl) acrylates and heteroaromatic analogues yielding substituted acenaphthenes and azaacenaphthenes. This highly functional-group-tolerant transformation was put to the test in an enantioselective formal synthesis of delavatine A. Mechanistic details were elucidated by DFT-calculations revealing an unusual intramolecular H-transfer mediated by a primary amine. The generality of this transformation enables a novel synthetic strategy of five membered ring annulation at an advanced stage, allowing reliance upon naphthalene chemistry up to the point of acenaphthene construction.

Acenaphthene **1** and acenaphthylene **2** occur as substructures in different chemical areas. Acenaphthene has been described as a "Cinderella" among coal-tar hydrocarbons due to its unique structure, photophysical properties and intriguing chemistry.[1] Because of these features, acenaphth(yl)ene derivatives have found application in different fields of chemistry including medicinal **3**,[2] environmental **4**[3] and materials[4] chemistry **6**. The motif is also present in the natural product delavatine A (**5**),[5] (Figure 1).

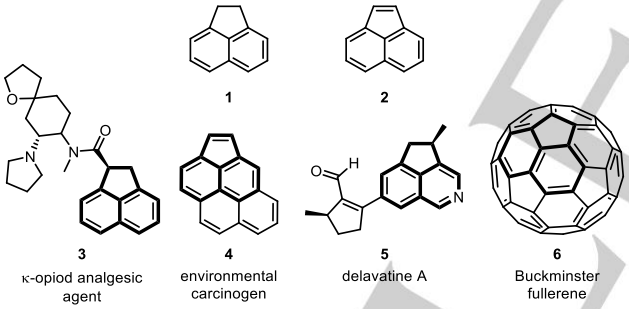
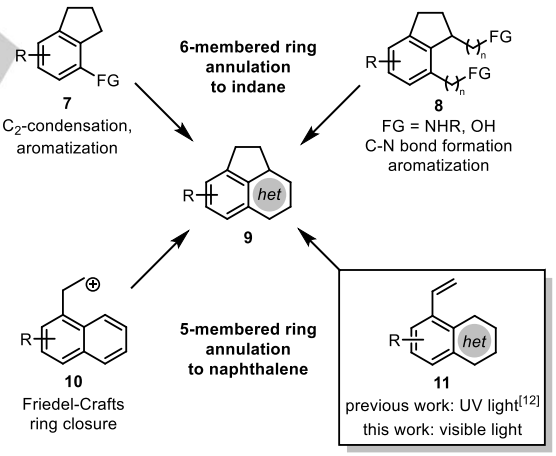


Figure 1. Acenaphthene **1** and acenaphthylene **2** as subunits in various structures **3**-**6** from different areas of chemistry.

Cyclopenta-fused polyaromatic hydrocarbons (CP-PAHs) are ubiquitous environmental carcinogens, emitted by combustion processes such as the burning of fossil fuels, making acenaphthene and acenaphthylene two of the 16 PAHs monitored by the EPA. As CP-PAHs represent some of the most stable forms of carbon, they are believed to be present in interstellar medium, detectable in diffuse interstellar absorption bands.[6] Acenaphthylenes are synthetically accessible by dehydrogenation of acenaphthenes.[7]

Substituted (aza)acenaphthenes **9** were previously obtained by annulation and aromatization of a six-membered ring to an indane **7** or **8** (Scheme 1).[5c, 8, 18] Naphthalenes, quinolines and isoquinolines are easily accessible building blocks, which render them good precursors for acenaphthenes. This makes annulation of the five-membered ring attractive from a retrosynthetical point of view, as it allows splitting of the acenaphthene into a naphthalene "core" and a C_2-"bridge". The most widely-used methods for this annulation are harsh, involving flash vacuum pyrolysis,[9] carbocations **10**[10] and related Friedel-Crafts acylations.[11] An annulation of the five-membered ring could also start from a vinyl naphthalene **11**. Here we show that a visible light mediated ring closure of substituted vinyl naphthalenes **11** is an efficient and functional-group-tolerant synthetic route to substituted acenaphthenes.



Scheme 1. Different synthetic routes to substituted acenaphthenes.

Given our group's past work in the synthesis of highly functionalized naphthalenes and natural products,[14] we sought to merge the field of naphthalene chemistry with the field of acenaphth(yl)enes by developing a general five-membered ring annulation and putting it to the test in a synthesis of delavatine A. We turned to photochemistry, as pioneering work of Lapouyade showed formation of a five-membered ring on similar under UV-irradiation in the presence of an excess of different amines in high dilution.[12] Acrylate **12a** was selected as a substrate for optimization of the photocyclization to **13a** (Table 1) as it carries

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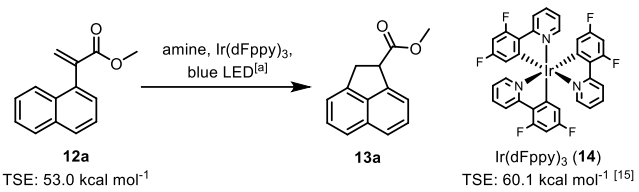
an ester as a synthetically versatile functional group on the double bond and its derivatives are readily available from 1-bromonaphthalenes by Stille cross-coupling with the appropriate acrylstannane (see Supporting Information). Usage of visible light by implementation of triplet-energy transfer was envisioned to provide a broad functional-group-tolerance and applicability in complex molecule synthesis. Calculation of the singlet-triplet excitation energy (TSE) of **12a** (53.0 kcal mol^{-1}, BP86/def2TZVPP) showed Ir(dFppy)$_3$ (**14**) to be an appropriate sensitizer excitable by visible light.

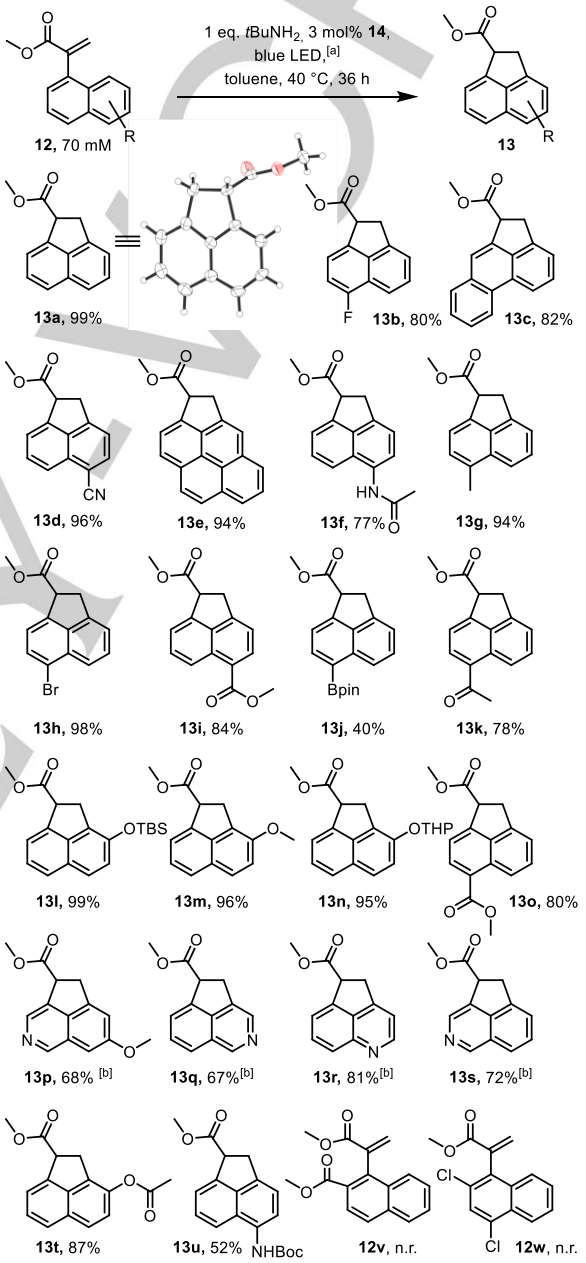
Table 1. Course of optimization



#	**14** [mol%]	amine	equiv. amine	solvent	*c* [mM]	*T* [°C]	*t* [h]	Yield [%] **13a**
1	5	Et_3N	5	MeCN	5	r.t.	48	<20
2	5	*t*BuNH$_2$	5	MeCN	5	r.t.	48	27[b]
3	3	*t*BuNH$_2$	5	toluene	5	r.t.	72	75
4	3	*t*BuNH$_2$	5	toluene	5	40	48	82
5	3	*t*BuNH$_2$	1	toluene	70	40	36	99

[a] Kessil A160WE (420-480 nm, see Figures S9 and S10 for emission spectra)
[b] 77 % *brsm*

Addition of a tertiary amine, e.g. Et_3N caused formation of byproducts, most likely due to photoredox chemistry of Ir(dFppy)$_3$ (entry 1). CV-measurements revealed *t*BuNH$_2$ as one of the most abundant primary amines unable to engage in redox chemistry with Ir(dFppy)$_3$ (Figures S1, S2). Substitution for Et_3N afforded only the desired product, albeit with low conversion (entry 2). Running the reaction in toluene (entry 3) and raising the temperature (entry 4) accelerated conversion, allowed loading of amine to be decreased to 1.0 equiv. and substrate concentration to be raised to 70 mM, resulting in formation of **13a** in quantitative yield (entry 5), see Supporting Information for optimization details (Table S1) and effects of deviation from standard conditions (Table S2). Formation of the five-membered ring was confirmed by single crystal X-ray diffraction.[16] After having identified the optimum conditions, the substrate scope of the photocyclization **12** → **13** was investigated (Scheme 2). As envisioned, implementation of visible light resulted in a variety of acenaphthenes bearing electron-donating as well as -withdrawing functional groups at different positions being formed in excellent yields. Synthetically valuable functionalities such as Bpin (**13j**) and bromide (**13h**), as well as different protecting groups, were also tolerated in the cyclization. Ring closure also occurred readily on polyaromatic compounds, furnishing CP-PAHs **13c** and **13e**, which are of potential interest to materials chemistry.[17] Heteroaromatic systems (**13p** - **s**) showed lower conversion under standard conditions and required more forcing conditions, possibly due to photophysical loss of energy. Substitution in 2-position is not tolerated, as it most likely inhibits adoption of the reactive conformation (**12v**, **12w**).



Scheme 2. Investigation of the substrate scope on the naphthyl ring. Isolated yields, 0.2 mmol scale, 2.85 mL toluene (70 mM). [a] Kessil A160WE (420-480 nm). [b] Reaction conditions: 15 equiv. *t*amylamine, 5 mol% Ir(dFppy)$_3$, blue LED,[a] 6.40 mL toluene (30 mM), 80 °C, 36 h.

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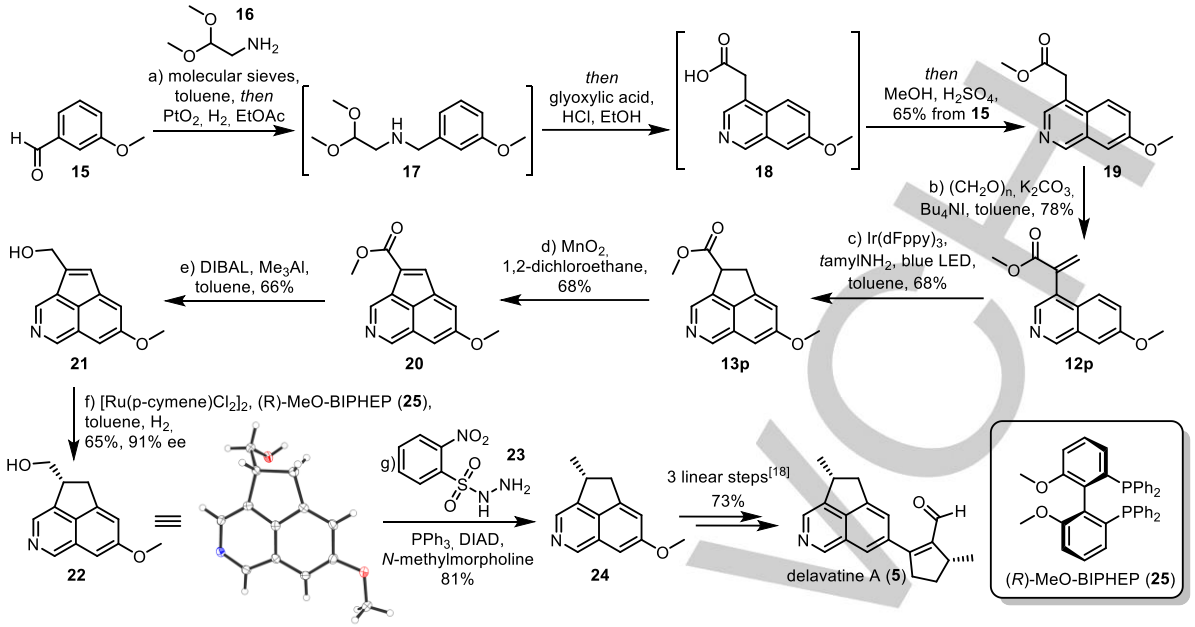

Scheme 3. a) aminoacetaldehyde dimethyl acetal (**16**, 1.0 equiv.), molecular sieves (3 Å), toluene, r.t., 4 h, then 1 mol% PtO_2, H_2 (1 bar), EtOAc,, r.t., 48 h, then glyoxylic acid (50% in water), 37% HCl/EtOH (1:1), reflux, 2 h, then H_2SO_4 (2.0 equiv.), MeOH, reflux, 18 h b) $(CH_2O)_n$ (3.2 equiv.), Bu_4NI (13 mol%), K_2CO_3 (3.1 equiv.), toluene, 80 °C, 18 h c) *t*amylNH_2 (15.0 equiv.), Ir(dFppy)$_3$ (5 mol%), toluene, Kessil A160WE (420-480 nm), 80 °C, 48 h d) MnO_2 (5.0 equiv.), 1,2-dichloroethane, 80 °C, 2 h e) DIBAL (2.2 equiv.), Me_3Al (1.1 equiv), toluene, -95 to -40 °C, 1 h f) [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), (*R*)-MeO-BIPHEP (**25**) (11 mol%), toluene, H_2 (100 bar), 60 °C, 18 h, g) NBSH (**23**, 3 equiv.), PPh_3 (2 equiv.), DIAD (2 equiv.), *N*-methylmorpholine, -30 °C (2 h) to r.t. (2 h).

With the substrate scope established, we turned our attention to the synthesis of delavatine A (**5**). Delavatine A was isolated in 2016 from the mountain flowering plant *Incarvillea delavayi* and showed considerable cytotoxic properties.[5a] As delavatine A had recently been synthesized by Li,[18] we chose intermediate **23** as a target to display the applicability of our novel retrosynthetic strategy, constructing the isoquinoline core first and building the bridge after, as shown in Scheme 3. Starting off with a Bobbitt-type isoquinoline synthesis[19] (**15** → **17** → **18**) and subsequent esterification, 3-methoxybenzaldehyde (**15**) was converted into ester **19**. Aldol condensation with formaldehyde under phase transfer conditions yielded acrylate **12p**. Under the developed forcing conditions, visible-light mediated cyclization of **12p** afforded azaacenaphthene **13p** in good yield. Dehydrogenation to azaacenaphthylene **21** was accomplished using MnO_2. The presence of a Lewis acid ($AlMe_3$) was found to suppress side reactions on the isoquinoline system in the reduction of **21**. As no precedence of enantioselective acenaphthylene hydrogenation was found, this transformation was developed for the synthesis of chiral alcohol **22**. Rhodium- and iridium-based catalysts allowed for mild conditions yet afforded low enantioselectivities. Synthesis of a ruthenium complex from ligand **25** and its usage in a hydrogenation under high pressure and temperature afforded an ee of 91%, after commercially available catalysts delivered unsatisfactory results (Table S4). The absolute configuration of resulting alcohol **22** was established as (*R*) by single crystal X-ray diffraction.[16] Deoxygenation[20] yielded azaacenaphthene **24**, the intermediate of Li's synthesis.[18] This protecting-group-free formal synthesis of delavatine A demonstrates the utility of visible-light photocatalysis in natural product synthesis[21] and represents a rare case of using acenapthylenes as intermediates. Having accomplished the formal synthesis, we became interested in the mechanism of the photocyclization. After confirming quenching of the triplet state of sensitizer **14** by acrylate **12a** through a Stern-Volmer quenching experiment (Figures S6, S7), running the reaction with standard triplet sensitizers instead of potentially redox-active Ir(dFppy)$_3$ also afforded product (Table S3). In conjunction with the previously performed CV-measurements (Figures S1, S2), a triplet energy transfer instead of a redox-based mechanism thus seems likely. To study the course of the reaction after sensitization, the mechanism (**12p** → **13p**) was studied using DFT-calculations (Figure 2). As indicated by aforementioned experiments, compound **12p** is most likely converted by sensitizer **14** from the singlet (S_0) ground state into the first excited triplet state (T_1). Ring closure to the 5-membered ring can occur on the triplet potential energy surface (PES) via transition state **TS** leading to intermediate **IM**. The rather delocalized nature of the unpaired electrons in **IM** is shown by the spin density (Figure S14). At this point, the necessary H-shift from **IM** to **13p** requires the amine. On the triplet PES a barrier of 130 kJ mol^{-1} (Figure S12) for the H-transfer was found, leading to an energetically less stable product **13p** (T_1). Instead, we found the amine to catalyze the reaction on the singlet PES resulting in a barrierless step from **IM** to **13p** (S_0). The amine thus acts as an intramolecular H-shuttle in the reaction (see the animated GIF in the Supporting Information).

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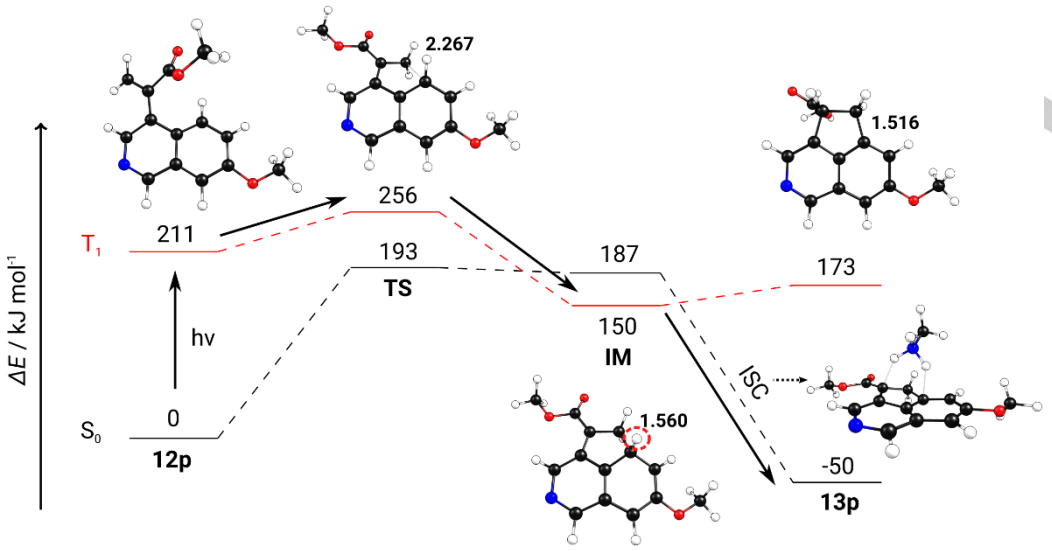

Figure 2. Mechanism of the photocyclization from **12p** to **13p** as elucidated by DFT-calculations (BP86, def2-TZVPP). Singlet (S_0) and triplet (T_1) potential energy surfaces are shown, arrows indicate the proposed reaction pathway. A structure (non-stationary point) along the amine-assisted H-transfer (circled atom) pathway is shown. Bold numbers designate C-C bond lengths.

In summary, we have reported a visible-light-mediated, highly functional-group-tolerant photocyclization which furnishes acenaphthenes. The cyclization is shown to proceed via an intramolecular amine-assisted H-transfer reaction by computational methods. A successful application in the synthesis of delavatine A demonstrates the utility of this new retrosynthetic disconnection, annulating the five- rather than the six-membered ring. This work paves the way for a widespread application of acenaphthenes and acenaphthylenes as intermediates in complex molecule synthesis, allowing their formation at an advanced stage. The broad substrate scope of the presented reaction also breaks ground for the implementation of substituted acenaphthenes as building blocks in different areas of chemistry, as it brings the synthesis of acenaphthenes into the realm of well-established naphthalene chemistry.

Acknowledgements

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Keywords: photochemistry • synthetic methods • natural products • acenaphthenes • delavatine A

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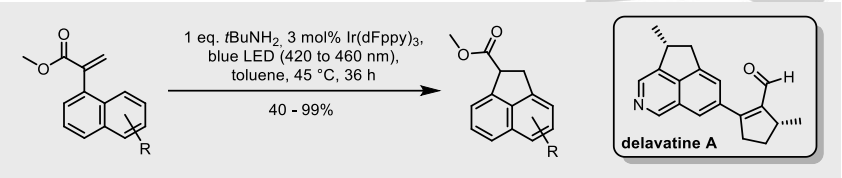

Hampered by harsh reaction conditions, the synthesis of functionalized acenaphthenes remains the key challenge in the exploration of their chemistry. Addressing this challenge, a visible light and amine-catalyzed photocyclization is reported. Elucidation of the mechanism using DFT-calculations and application in a formal synthesis of (+)-delavatine A pave the way for further application.

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